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Dean, Temple School of Pharmacy
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of Colleges of Pharmacy

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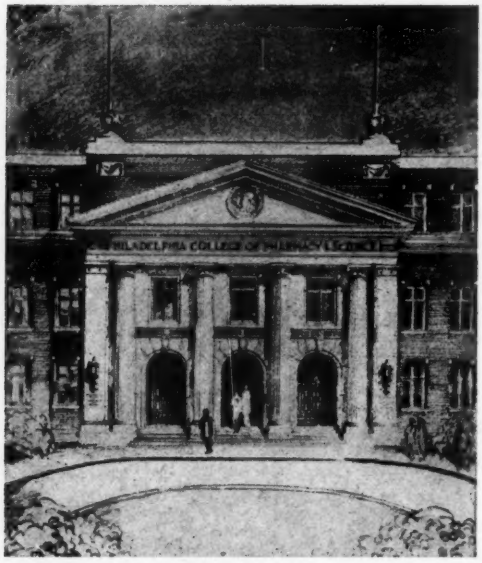

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OUR COVER

DR. H. EVERT KENDIG

IN the field of pharmaceutical education Dean Kendig is noted for his untiring efforts to raise and strengthen the standards of pharmaceutical education. Dr. Kendig graduated from the School of Pharmacy of Medico-Chirurgical College, Philadelphia, in 1901 and later received his M. D. there in 1905. In 1910 Temple University bestowed on him the degree Doctor of Pharmacy. Dr. Kendig has been Professor of Pharmacy and Public Health since 1907 and Dean of the Pharmacy School for nine years. His activities both past and present are varied and his contributions to pharmacy are well known and appreciated.

Dr. Kendig's services as the Chairman of the Joint Committee on the Status of Pharmacists in the Government services have helped greatly in bringing to the attention of the authorities the proper position that Pharmacy should occupy in our national defense effort.

As the retiring president of the American Association of Colleges of Pharmacy he has, during the past year, discharged his responsibilities in a most creditable fashion. Probably never before has this office been so burdened with difficulty, and only one so dynamic as Dr. Kendig could have met this challenge.

EDITORIAL

LET US HAVE FAITH

TO many persons engaged in the health sciences the present world chaos has resulted in a deadening sense of futility and depression which makes continued effort at best very difficult. The training of physicians, dentists, nurses and pharmacists has one common and distinguishing quality which sets them quite apart from all other fields of human endeavor, unless it be the ministry. This is a dedication to the relief of human suffering, and unless the individual practicing his profession is motivated by this basic aim, disregarding all others, it cannot be said that his career in his chosen field is a success.

Again we find that the constructive forces of humanity, of which we are a part, have been detoured, as it were, and a premium placed on man's ingenuity to create better and more terrible implements of destruction. In the space of a few days we learn of casualties which probably offset months of effort on our part, in normal times, to heal, comfort and prolong life.

Let us not, however, fall victim to a mental impasse which, if permitted, would still further increase the tragedy and scope of human suffering. Now, more than ever before, we should exercise our every talent in the direction of our profession, since one of the tolls of modern warfare is the prevalence of disease and illness, not only amongst the armed forces but throughout civilians alike. Only by increased and intensified service can we maintain the status of public health on a level with that which we have been enjoying. Without greater effort on our part we are certain to go backward and see incidence of disease rising and many valuable gains lost.

Our position now is similar to that of an oarsman rowing against a swift current; the task is indeed difficult and progress seems slow, yet, with the changing tide a reversal in the direction of the current is inevitable. Constructive influences will again predominate, social progress and well-being again will be the keynote of world economy, and the saving of lives will be more important than their destruction.

Let us have faith in the future; man's progress has ever been upward. Charity, love and kindness will surely some day be the code by which men live and nations devise their international policy.

L. F. TICE.

BACTERICIDAL AND BACTERIOSTATIC PROPERTIES OF SURFACE TENSION DEPRESSANTS

The following is another in a series of papers on studies conducted by Dr. Gershenfeld and associates relating to the bactericidal and bacteriostatic properties of various wetting agents. In this paper the authors correlate the effect of several factors: type of compound (whether cationic or anionic), hydrogen-ion concentration, and organism employed. Wide differences in behavior are found based on a variance of the above conditions.

By Louis Gershenfeld and Vera Elaine Milanick

Department of Bacteriology,
Philadelphia College of Pharmacy and Science.

Historical Consideration

THE demands of industry for wetting agents and detergents to meet a variety of special purposes have led to a very rapid commercial development of these compounds. More than a thousand wetting agents and detergents have been patented in the past decade (1). Recently great interest in organic compounds possessing in particular the property of surface activity in aqueous systems have developed. The chemical structure of these compounds and the relation of their molecular structure to properties of interfacial tension are being studied more carefully and are better known. Data concerning these compounds have been meager, though some information embodied in reports on the enhancement of the bactericidal properties of antiseptics by the addition of surface tension depressants is available (2) (3).

Surface Tension

Berczeller (1917) was probably the first to point out the significance of surface tension in the inactivation of biological substances (4). Larson, Cantwell, and Harzell (1919) studied the effect of lowered surface tension on the growth and characteristics of certain organisms and concluded that the growth of bacteria in ordinary broth was greatly influenced by the surface tension of the medium (5). Larson (1921) (6) continued this work and discovered the limit of surface

tension in the growth of pneumococcus, streptococcus, and B. anthracis. He discovered that the intestinal bacteria grew well at a lowered surface tension. The concentration of the colon-typhoid group of bacteria at the surface of the medium was attributed to the concentration of the surface-acting material at the surface.

The work of Marshall (1924) showed that the surface tension of infusion broth used to prepare synthetic media is not affected as a consequence of bacterial growth. Organisms growing in media of different surface tensions produce varying quantities of gas as the end-result of metabolism (7). Frobisher noted that surface tension is an important factor in bacterial growth, and in morphology, cell division, and cell grouping (3).

Mellon, Hastings and Anastasia (1924) studied the cohesive power responsible for the spontaneous agglutinability of certain bacteria. They found that this power could be diminished or entirely eliminated by varying the surface tension of the solution (8). In recent years, Marshall and Robinson (9) have studied the relation of surface tension to diphtheria toxin production. Broth having a surface tension as low as 35 dynes inhibited pellicle formation completely and prevented the growth of the organism.

A theoretical consideration of the phenomena of surface tension shows how depressants can have practical application in relation to antisepticity. Surface tension is defined as the force in dynes acting across a unit length in the surface required to stretch that surface (10). If the bacteria in the process of fission are looked upon as an oil drop pinching in two in the center, it can readily be seen how a slight increase in interfacial tension would tend to stimulate the process, while a considerable decrease would prevent it (6).

The bacterial cell is enclosed by a semi-permeable membrane which is easily susceptible to external changes (2). Substances which reduce the surface tension become concentrated on the bacterial surface, affecting the permeability of the membrane and thus increasing the diffusability through the cell. Petroff and Schain state, "Morphology, reproduction and numerous physico-chemical and immunological reactions are conditioned by the ions and other compounds absorbed by the cell surface" (2). If we can upset the balance of the surface tension of the bacterial cell perhaps the cell can be more readily penetrated, thus inactivating the power of reproduction and finally destroying it.

Soaps

Upon this premise two classes of compounds have found application: soaps and synthetic compounds, the so-called wetting agents. Soap is the term ordinarily used to designate the alkaline salts, sodium, potassium and ammonium, of the non-volatile fatty acids, beginning with those containing 8-carbon atoms. Strictly speaking, all metallic salts of fatty acids are soaps, but the salts of the alkaline metals and ammonium are the only ones which are appreciably soluble in water, and consequently the ones commonly used as cleansers (11).

Chevreul (1823) ascribed the detergent value of soap solutions to their emulsifying actions upon fats. Fifty-six years later Quincke stated that the emulsified droplets of oil are surrounded by thin layers of soap which prevent coalescence and thereby stabilize the emulsion (12): and in 1903, Hillyer showed that the latter was a function of the lowering of the oil-water interfacial tension (13). An extensive series of studies on the nature of soap solutions has been reported by McBain and associates from 1910 to 1920 (14) (15).

The bactericidal and bacteriostatic action of soaps and certain naturally occurring detergents has been recognized for years. Since Robert Koch first found that soap solutions possessed bactericidal properties, a considerable literature has accumulated concerning the subject. Reichenbach (1909) first studied the bactericidal action of soaps using E. coli as the test organism (16).

Walker (1925) stated that the germicidal properties of soaps and the resistance of bacteria may be more closely correlated in the future with surface tension. He conducted some interesting experiments on the bactericidal action of soaps and found that only the higher soaps (i. e., colloidal soaps) are bactericidal. Walker advised that lathering the hands for three minutes with a cocoanut-oil soap solution will kill bacteria such as the diphtheria and colon bacilli, gonococci, pneumococci, and typhoid bacilli (17).

Eggerth studied the bactericidal action of alpha substituted soaps. He found that the soaps of the alpha bromo fatty acids were usually more bactericidal than the unsubstituted soaps (18). Stuart and Pohle found that rosin soap solutions and their mixtures with fatty acid soaps were more active than the corresponding fatty acid soaps alone and also that cocoanut-oil soap was germicidally more active against E. coli and Eberthella typhi than other soaps made from natural fats and oils (44). Two main factors determine the bactericidal

action of a soap: its ability to penetrate into the bacterial cell and its toxic action upon the bacterial protoplasm after it has penetrated. As the number of carbon atoms in the soap molecule increases, the toxicity becomes greater but the power to penetrate into the cell diminishes (19).

Soaps have certain undesirable characteristics which limit their usefulness. Ordinary soaps have a too alkaline reaction for application on sensitive tissue. They also are precipitated by hard water. The new types of depressants studied are, in most cases, superior to soaps in wetting and cleansing ability and are more stable in acid and alkaline solutions (20). In this research, the term "surface tension depressants" is applied to these synthetic compounds which also are spoken of by various workers as wetting agents, surface tension reducents, and detergents.

Three important agents or factors concerned in an environment to obtain a bactericidal effect are:

1—the surface active material;
2—the specific organism;
3—the hydrogen-ion concentration of the environment.

The influence of these agents or factors on the resultant bactericidal and bacteriostatic efficiency must be considered if a comparison is to be made of the different surface tension depressants.

Hydrogen-ion Concentration of the Environment

It has been recognized for some time that the hydrogen-ion concentration plays an important part in influencing the growth of bacteria. Eggerth clearly demonstrated the effect of pH changes on the bactericidal action of soaps. He found that the lower members of the saturated series of soaps were more bactericidal in an acid environment while the longer chained soaps were more bactericidal at an increased pH (19). Investigators have found that an increase of the pH favors the disinfecting power of basic dyes and a decrease favors the bactericidal activity of acid dyes (21). Troube (22) found that sodium carbonate accentuates the activity of crystal violet, and Promazec (23) noted an increased staining effect of methylene blue with an increase of acidity. Dernby and David stated that eucupin and quinine alkaloids are more effective against the staphylococcus and diphtheria bacillus in solutions which are alkaline (24).

Dunn reported that alkyl dimethyl benzyl ammonium chloride (Zephiran) exerts a greater bactericidal action at an alkaline pH (25).

Cetyl pyridium chloride was found highly bactericidal for virulent organisms by the F. D. A. method and the effect of changes of pH on its activity was studied and compared with well-known bactericides (26). Browning, Gubransen and Kennaway found that the bactericidal effect of diaminoacridine methyl chloride is increased 100 times by a change of pH of from 4 to 11 (27). There are, however, few known organisms which have a natural pH range of growth as wide as suggested by this author. In studying the pH effect of bactericidal action, it is essential to conduct the investigation within the limits of bacterial growth, preferably within the range of pH 5 to 9.

Gershenfeld and Perlstein in their study on the significance of hydrogen-ion concentration in the evaluation of the bactericidal efficiency of Aerosol OT, reported that Aerosol OT exerted a marked increase in bactericidal efficiency with an increase in the H- ion concentration (28).

The pH effect may be due to one or several factors. Various thoughts have been expressed. The data published by Baker, Harrison and Miller reveals that the pH activation "is in the direction which could favor formation of undissociated molecules, and may be more effective than ions because of greater ability to enter the cell" (20). These same workers further state that, "it is possible that hydrogen-ion concentration directly affects the bacteria, altering either membrane or protoplasm in such a manner as to render the micro-organisms more susceptible to the action of the surface tension depressants" (20). Osterhout indicates that undissociated molecules penetrate more readily into protoplasm than ions (29).

The effect of the pH may be due to alterations of the solubility of the reducing agent in the aqueous phase or in the bacterial protoplasm. The decrease in surface tension increases the concentration of the depressant at the surface of the bacteria. This would effect the distribution coefficient of the depressant between the organism and the test fluid. The changes which occur in the pH of living bacterial protoplasm when the pH of the outside fluid is altered, are not known (30). It is apparent that special attention must be given to control of hydrogen-ion concentration in any studies on the bactericidal and bacteriostatic properties of surface tension depressants.

The Specific Organism in the Environment

Soaps and related compounds have an unusual affinity for specific micro-organisms, or closely related groups of bacteria. Many workers

have shown that certain soaps sharply differentiate between Gram-positive and Gram-negative organisms. Avery demonstrated the selective bactericidal action of soap on micro-organisms, and recommended for the isolation of influenza bacilli a medium containing sodium oleate (31). The work of Walker indicated that staphylococci are very resistant to certain soaps although pneumococci and streptococci are usually susceptible (32).

Eggerth (1926) found that the brominated soaps of 10 and 14 carbon atoms were more bactericidal for Gram-negative organisms while soaps of 16 and 18 carbon atoms displayed greater bactericidal efficiency for Gram-positive organisms. He also found that the toxicity of the brom soaps for all species of bacteria increases rapidly with the length of the fatty acid chain. The ability to penetrate into the bacteria however diminishes with equal rapidity. Bacteria vary considerably in the permeability of their limiting membranes. The Gram-negative organisms were found to be less permeable than the Gram-positive bacteria (33).

Stearn found that Gram-negative organisms have a greater tendency to retain acid dyes than Gram-positive bacteria. The staphylococcus was found to retain the basic dye from a pH range of 3 and higher while E. coli only began to retain it to any extent at a pH of 8 and higher (34). Hittche found that the unsaturated soaps such as oleate, linoleate, and linolenate were bactericidal toward the staphyloccus but not toward the colon bacillus (35).

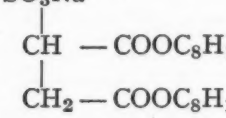
Composition of Surface Active Material

Closely related to the significance of the species of micro-organisms to bactericidal activity is the structure of the surface depressant employed. Rideal stated that results dependent upon changes due to surface energy might readily be affected by differences in structure of the molecule responsible for the surface effects (36). Katz and Lipsitz obtained results which indicated that surface-active properties associated with chemicals possessing a cyclic structure are more effective in inhibiting growth than those possessing long aliphatic chains (37).

From the chemical standpoint surface tension depressants can be classified in three main groups (20).

1—Anionic surface active compounds, which have the active or non-polar portion of the molecule carrying a negative charge (38).

Example: Aerosol OT — di-octyl sodium sulfosuccinate

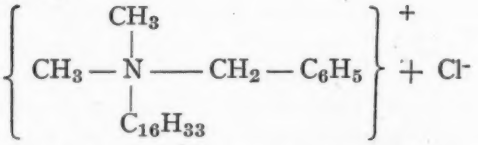


which ionizes with the hydrophobic group in the anion as follows:

$$Na^+ + C_{20}H_{37}O_4SO_3^-$$

2—Cationic surface active compounds, which have the active or non-polar portion of the molecule carrying a positive charge (38).

Example: Triton K-12—Cetyl dimethyl benzyl ammonium chloride.



3—Non-ionized compounds, such as the polyglycerol esters.

Baker, Harrison and Miller have studied the ionic configuration of the surface depressant molecules. In their work on the effect of synthetic detergents on respiration and glycolysis by the manometric technique, they have shown that cationic or anionic structure, as well as hydrocarbon chain length, are important factors in determining the relationship between chemical structure and the effects on bacterial metabolism. Their summarized data indicated that cationic detergents exhibited the maximum activity in the alkaline pH and affected both Gram-positive and Gram-negative organisms. The anionic detergents had the maximum activity in the acid range and inhibited the metabolism of Gram-positive micro-organisms (20). For additional historical data, references are found in other articles by one of us (28) (43) (45).

Purpose

This investigation was undertaken to determine whether or not the surface tension depressants studied are bactericidal or bacterio-

static. The experiments were designed to correlate the following three important agents or factors in their application to the bactericidal and bacteriostatic effects:

1—the surface active material;

2—the hydrogen-ion concentration of the environment;

3—the specific organism.

The molecular structure of the surface tension depressant was first considered. The problem was approached by classifying the depressants according to their ionizing ability—that is, anionic or cationic compounds.

In close relation to the chemical structure of the surface tension depressant, the significance of its affinity for specific micro-organisms was considered. The selected depressant was studied to observe any difference in effect upon bacteria, depending whether a Gram-positive or a Gram-negative organism was used. The two organisms, Staphylococcus aureus and Eberthella typhi, were selected since the depressants were tested by the Food and Drug Administration Phenol Coefficient Method and standard strains of these two organisms were available.

In adjusting the pH of the environment, which comprised the aqueous solution of the depressant, the diluent water, and the broth culture of the organism, the effect of the change in the hydrogen-ion concentration was noted. From this data, the range of pH wherein the depressant exerted its maximum efficiency was sought.

Procedure

Material and Methods

The surface tension agents used are noted in Table I.

A—Sterility Test on the Depressants

One per cent. aqueous solution of all eight depressants were made with sterile distilled water under aseptic conditions. One-half cc. of the solution was transplanted into 100 cc. of sterile F. D. A. broth and incubated at 37 degrees C. for 24 hours. Solutions showing growth in the broth were discarded.

B—Surface Tension Measurements

The surface tension measurements of the 1 per cent. aqueous solutions of the eight depressants studied were obtained by the DuNuoy Tensiometer. Findings—The 1 per cent. solutions of the eight depressants studied did not show any marked difference in surface tension. The surface tension ranged from 26-31 dynes per cm. at 25 degrees C.

C—Adjustment of the pH

The pH of the stock solution (1:100 dilution) of all the surface tension depressants (with the exception of Triton), the sterile distilled water, and the test organism were adjusted colorimetrically (39). The adjustments were made with N or N/10 HCl and NaOH. At the completion of each test the pH of the final mixture was rechecked.

In testing Triton K-12, it was found that the pH of the aqueous solution could not be adjusted by the colorimetric method due to its colloidal nature. Therefore two other methods were used:

1—Hydrogen electrode method (10).
2—Buffer solution method.

Basic acid solution
Boric acid —12.4 gm.
KCl — 7.4 gm.
Distilled H_2O—1000 cc.

Basic alkaline solution
Na_2CO_3(anhyd.)— 21.2 gm.
Distilled H_2O — 1000 cc.

pH of resulting buffer solution	cc. basic acid solution	cc. basic alkaline solution
5	30	0
6	30	0.05
7.2	30	1
8.2	30	3
9.0	30	8

The buffered solution at the desired pH was used, instead of distilled water, in making the desired dilution of Triton K-12.

NOTES—Fresh 1 per cent. aqueous solutions of the depressants were made at the beginning of each test, with the exception of the Aerosols. The 1 per cent. solutions of the Aerosols were made 5 to 6 hours before use on account of their slow solubility. Tergitol 4, 4T, and 08, Nopco D. L. N. and Triton K-12 dissolved quickly in water and were prepared immediately before the tests were started.

Concentrations stronger than 1:100 were not tested, because in this investigation an attempt was made to show a comparison of bactericidal efficiencies of identical strengths which would be dilutions apt to be employed in practice.

Technique

The Food and Drug Administration Phenol Coefficient Method (40) was used. The test organisms were 22-26 hour old cultures of Eberthella typhi (Hopkin's strain), and Staphylococcus aureus (F. D. A. strain) incubated and grown in F. D. A. broth at 37 degrees C. The test culture was transferred daily in F. D. A. media for not more than one month. At the end of each month, a fresh transfer was made from the stock culture. The stock culture was carried on F. D. A. agar and transferred once a month. When the test organism had not been transferred daily, four or five consecutive daily transfers were made in broth before using.

The selected dilutions of the surface tension depressant were made with sterile distilled water. In all the tests, the resistance of the culture organism was assured by control tests. The control tests consisted of: 1:80 and 1:90 dilutions of phenol for Staphylococcus aureus, and 1:100 and 1:110 dilutions of phenol for Eberthella typhi, prepared from a standard 5 per cent. phenol solution.

The seeding tubes containing the dilutions were placed in the water bath at 37 degrees C. for 5 minutes until the temperature of the bath was reached. To each of the dilutions, at a time interval at which the transfers were to be made, 0.5 cc. of the shaken unfiltered test culture was added. Transplants of one standard loopful were made at the end of 5, 10, and 15 minutes into 10 cc. of sterile F. D. A. broth. All tests were conducted at a temperature of 37 degrees C.

The tubes were incubated at 37 degrees C. for 48 hours. At the end of that time the tubes were read for the effective killing dilution, which is the highest dilution from which transfers failed to produce growth.

Bacteriostatic Test

Four standard loopfuls of all tubes that failed to show growth were transferred into 100 cc. of F. D. A. broth to test for bacteriostatic action. Growth in the 100 cc. of broth after incubation for 48 hours at 37 degrees C. indicated bacteriostatic action.

The findings are presented in the tables that follow.

Table I

Trade name	*Chemical Composition*	*Manufacturer*
Aerosol OT	Di-octyl sodium sulfosuccinate	American Cyanimid & Chemical Corp.
Aerosol AY	Di-amyl sodium sulfosuccinate	American Cyanimid & Chemical Corp.
Aerosol MA	Di-hexyl sodium sulfosuccinate	American Cyanimid & Chemical Corp.
Tergitol 4*	Sodium tetra-decyl sulfate	Carbon and Carbide Corp.
Tergitol 4T*	Triethanolamine tetra-decyl sulfate	Carbon and Carbide Corp.
Tergitol 08**	Sodium octyl sulfate	Carbon and Carbide Corp.
Triton K-12	Cetyl dimethyl benzyl ammonium chloride	Röhm and Haas
Nopco D. L. N.	High SO_3 sulfonated Oil	National Oil Products Co.

Anionic Compounds	*Cationic Compound*
Aerosol OT	Triton K-12
Aerosol AY	
Aerosol MA	
Tergitol 4	
Tergitol 4T	
Tergitol 08	

Table II

AEROSOL OT

Staphylococcus aureus—37°C.

pH	7.0			6.0			pH	5.0			4.0		
time	5	10	15	5	10	15	time	5	10	15	5	10	15
dilution							dilution						
1:100	+	+	+	0	0	0	1:10,000	0	0	0	0	0	0
1:500	+	+	+	0	0	0	1:15,000	0	0	0	0	0	0
1:1000	+	+	+	0	0	0	1:20,000	0	0	0	0	0	0
1:2000	+	+	+	0	0	0	1:25,000	0	0	0	0	0	0
1:3000	+	+	+	0	0	0	1:30,000	0	0	0	0	0	0
1:4000	+	+	+	0	0	0	1:35,000	+	+	+	0	0	0
1:5000	+	+	+	+	0	0	1:40,000	+	+	+	+	+	+
1:6000	+	+	+	+	+	0	phenol	pH not adjusted					
1:7000	+	+	+	+	+	+	1:80	+	0	0			
phenol	pH not adjusted						1:90	+	+	0			
1:80	+	0	0										
1:90	+	+	0										

*Commercial Tergitol 4 & 4T used have a 25% active ingredient content.
**Commercial Tergitol 08 used has a 40% active ingredient content.

Table III

AEROSOL OT

Eberthella typhi—37° C.

pH	4.0			5.0			6.0			7.0		
time	5	10	15	5	10	15	5	10	15	5	10	15
dilution												
1:100	0	0	0	0	0	0	+	+	+	+	+	+
1:500	0	0	0	+	+	+	+	+	+	+	+	+
1:1,000	0	0	0	+	+	+	+	+	+	+	+	+
1:5,000	+	0	0	+	+	+	+	+	+	+	+	+
1:8,000	+	+	+	+	+	+	+	+	+	+	+	+
1:10,000	+	+	+	+	+	+	+	+	+	+	+	+
phenol	pH not adjusted											
1:100	+	0	0									
1:110	+	+	+									

Discussion

Aerosol

Preliminary tests were conducted on Aerosol OT, MA, and AY, using the Phenol Coefficient Method with Staphylococcus aureus, 37 degrees C. at pH 6. Aerosol OT displayed a bactericidal effect at 1:5000 (killed in 10 but not in 5 min.), while Aerosol MA and AY (also anionic compounds) revealed inefficiency even in 1 per cent. concentrations at the same pH (pH 6). Aerosol MA and AY are inferior to OT at pH 6 due, in all probability, to the fact that because of their lower molecular weight, they have less surface activity in ordinary water compared to Aerosol OT (41). Aerosol OT was therefore selected as representative of the Aerosols for further investigation.

Aerosol OT ionizes with the active portion of the molecule carrying the negative charge. This would classify it as an anionic compound. Table II indicates that the bactericidal action of Aerosol OT against Staphylococcus aureus is increased by a decrease in pH. This finding also was presented previously (28).

at pH 7—1:100 Aerosol OT does not kill within 15 min.
at pH 6—1:4,000 Aerosol OT kills within 5 min.
at pH 5—1:30,000 Aerosol OT kills within 5 min.
at pH 4—1:35,000 Aerosol OT kills within 5 min.

Table III shows a marked change in efficiency of Aerosol OT when tested against Eberthella typhi, a Gram-negative organism. However even here there is an increase in bactericidal action with a decrease in pH.

at pH 7—1 :100 Aerosol OT does not kill within 15 min.
at pH 6—1 :100 Aerosol OT does not kill within 15 min.
at pH 5—1 :100 Aerosol OT kills within 5 min.
at pH 4—1 :1,000 Aerosol OT kills within 5 min.

All bacteriostatic tests on Aerosol OT proved negative.

Table IV

TERGITOL 4 & 4T*

Staphylococcus aureus—37° C.

pH	4.0			5.0			6.0			7.0		
time	5	10	15	5	10	15	5	10	15	5	15	15
dilution												
1 :1000	0	0	0	0	0	0	0	0	0	+	0	0
1 :2000	0	0	0	0	0	0	0	0	0	+	+	+
1 :3000	0	0	0	0	0	0	+	+	0	+	+	+
1 :4000	0	0	0	0	0	0	+	+	+	+	+	+
1 :5000	0	0	0	+	0	0	+	+	+	+	+	+
1 :6000	0	0	0	+	+	0	+	+	+	+	+	+
1 :7000	0	0	0	+	+	0	+	+	+	+	+	+
1 :8000	+	0	0	+	+	+	+	+	+	+	+	+
1 :9000	+	0	0	+	+	+	+	+	+	+	+	+
1 :10,000	+	+	+	+	+	+	+	+	+	+	+	+
phenol	pH not adjusted											
1 :80	+	0	0									
1 :90	+	+	0									

*Commercial Tergitol 4 & 4T used have a 25% active ingredient content. Where comparisons are to be made in terms of 100% active ingredient, multiply the dilutions in this table by 4.

Table V

TERGITOL 4 & 4T*

Eberthella typhi—37° C.

pH	4.0			5.0			6.0			7.0		
time	5	10	15	5	10	15	5	10	15	5	10	15
dilution												
1:100	0	0	0	0	0	0	+	+	+	+	+	+
1:200	0	0	0	+	0	0	+	+	+	+	+	+
1:300	0	0	0	+	+	+	+	+	+	+	+	+
1:400	+	0	0	+	+	+	+	+	+	+	+	+
1:500	+	+	0	+	+	+	+	+	+	+	+	+
1:600	+	+	0	+	+	+	+	+	+	+	+	+
1:700	+	+	+	+	+	+	+	+	+	+	+	+
1:800	+	+	+	+	+	+	+	+	+	+	+	+
phenol	pH not adjusted											
1:100	+	0	0									
1:110	+	+	0									

Discussion

Tergitol

Tergitols ionize with the active portion of the molecule carrying the negative charge. This would classify them as anionic compounds. Tergitol 4, 4T, and 08 were tested against Staphylococcus aureus, and Eberthella typhi at 37 degrees C. with the pH ranging from 4 to 7.

Tergitol 08 revealed no bactericidal or bacteriostatic effect against Staphylococcus aureus or Eberthella typhi at pH 4 to 7.

Tergitol 4 and 4T showed an increase in bactericidal action when the pH was decreased, as is indicated in Tables IV and V.* When tested against S. aureus the following results were obtained (see Table IV):

at pH 7—1:100 Tergitol 4 and 4T kills within 10 min., but not in 5 min.
at pH 6—1:2,000 Tergitol 4 and 4T kills within 5 min.
at pH 5—1:4,000 Tergitol 4 and 4T kills within 5 min.
1:5,000 Tergitol 4 and 4T kills within 10 min.
at pH 4—1:7,000 Tergitol 4 and 4T kills within 5 min.
1:9,000 Tergitol 4 and 4T kills within 10 min.

Table V indicates a decrease in the efficiency of Tergitol 4 and 4T when tested against Eberthella typhi. However even here there is an increase in bactericidal action with a decrease in pH.

*Commercial Tergitol 4 & 4T used have a 25% active ingredient content. Where comparisons are to be made in terms of 100% active ingredient, multiply the dilutions given here by 4.

at pH 6 or higher the 1 :100 Tergitol 4 and 4T do not kill within 15 min.
at pH 5—1 :100 Tergitol 4 and 4T kills within 5 min.
1 :200 Tergitol 4 and 4T kills within 10 min.
at pH 4—1 :300 Tergitol 4 and 4T kills within 5 min.
1 :400 Tergitol 4 and 4T kills within 10 min.

All bacteriostatic tests on Tergitol 4 and 4 T proved negative.

Table VI

TRITON K-12

Staphylococcus aureus—37°C.

pH	4.0			5.0			6.0			7.2			8.2			9.0		
time	5	10	15	5	10	15	5	10	15	5	10	15	5	10	15	5	10	15
dilution																		
1 :100	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 :200	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0
1 :300	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0
1 :400	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0
1 :500	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0
1 :600	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0
1 :700	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0
1 :800	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0
1 :900	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1 :1000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1 :2000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1 :3000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1 :4000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :5000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :6000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :7000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :8000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :9000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :10,000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :12,000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1 :14,000	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0
1 :16,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0
1 :18,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0
1 :20,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0
1 :25,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0
1 :30,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0
phenol	pH not adjusted																	
1 :80	+	0	0															
1 :90	+	+	0															

Table VII

TRITON K-12

Eberthella typhi—37°C.

pH	4.0			5.0			6.0			7.2			8.2			9.0		
time	5	10	15	5	10	15	5	10	15	5	10	15	5	10	15	5	10	15
dilution																		
1:100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1:200	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1:300	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1:400	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0
1:500	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0
1:600	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0
1:700	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0
1:800	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0
1:900	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0
1:1000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1:2000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1:3000	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0
1:4000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:5000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:6000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:7000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:8000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:9000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:10,000	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0
1:12,000	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0
1:14,000	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0
1:16,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0
1:18,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0
1:20,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0
1:25,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0
1:30,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0
1:40,000	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
phenol	pH not adjusted																	
1:100	+	0	0															
1:110	+	+	+															

Discussion

Triton

Triton K-12 was selected from among the other Tritons due to the fact that it is more stable, more soluble in water, and less colloidal (42). Triton K-12 ionizes with the active portion of the molecule carrying the positive charge. This would classify it as a cationic compound.

Table VI indicates that the bactericidal action of Triton K-12 with Staphylococcus aureus is increased by an increase in the pH.

at pH 4	—1 :100	Triton K-12 does not kill within 15 min.
at pH 5	—1 :100	Triton K-12 kills within 5 min.
at pH 6	—1 :300	Triton K-12 kills within 5 min.
	1 :400	Triton K-12 kills within 10 min.
at pH 7.2	—1 :800	Triton K-12 kills within 5 min.
	1 :900	Triton K-12 kills within 10 min.
at pH 8.2	—1 :9,000	Triton K-12 kills within 5 min.
	1 :12,000	Triton K-12 kills within 10 min.
at pH 9	—1 :18,000	Triton K-12 kills within 5 min.
	1 :20,000	Triton K-12 kills within 10 min.

Table VII shows that Triton K-12 possesses a slightly increased bactericidal efficiency against Eberthella typhi as compared with Staphylococcus aureus.

at pH 4	—1 :100	Triton K-12 kills within 5 min.
at pH 5	—1 :200	Triton K-12 kills within 5 min.
at pH 6	—1 :400	Triton K-12 kills within 5 min.
at pH 7.2	—1 :800	Triton K-12 kills within 5 min.
at pH 8.2	—1 :10,000	Triton K-12 kills within 5 min.
at pH 9	—1 :18,000	Triton K-12 kills within 5 min.

The slight increase in the efficiency that occurs when Eberthella typhi is used as compared with Staphylococcus aureus is in all probability due to the fact that Staphylococcus aureus is the more resistant organism.

All bacteriostatic tests on Triton K-12 proved negative.

Discussion

Nopco DLN

Nopco DLN, in dilutions of 1 :100 or in weaker concentrations, showed no bactericidal or bacteriostatic action against Staphylococcus aureus or Eberthella typhi in a pH range from 4 to pH 9.

Discussion (General)

The bactericidal action of the depressants tested is not due apparently to a reduced surface tension. All of the 1 per cent. aqueous solutions of the depressants possessed approximately the same surface tension, yet Nopco DLN and Tergitol 08 did not reveal bactericidal action. The property of surface tension reduction as found in Aerosol OT, Tergitol 4 and 4T, and Triton K-12 appears to be independent of any bactericidal properties they display. Theoretically the reduction in surface tension seems to make the cell more penetrable, thus enabling the surface-active compound to enter the cell and inactivate it. But independent of any surface tension reduction the surface-active compound must, in the first place, be of such composition as to possess in itself a bactericidal effect if the latter action is desired. The difference in the findings obtained with Nopco DLN and Tergitol 08 as compared with Aerosol OT, Tergitol 4 and 4T, and Triton K-12 is due in all probability to a difference in chemical structure.

The molecular structure of the depressants is to be noted when the hydrogen-ion concentration of their solutions is considered. From the results obtained, it is revealed that the cationic compound Triton K-12 is most effective on the alkaline side while the anionic compounds Aerosol OT, Tergitol 4 and 4T are most effective on the acid side. It is apparent from the results obtained that special attention must be given to the control of the hydrogen-ion concentration in any study on the bactericidal property of depressants. Similar findings were recently reported by Gershenfeld and Perlstein (43).

Summary

Sterility tests, and bacteriostatic and bactericidal tests employing the F. D. A. Phenol Coefficient Method were conducted on the following surface tension depressants: Aerosol OT, MA and AY, Tergitol 4, 4T and 08, Triton K-12 and Nopco DLN. Fresh 1 per cent. solutions of the depressants were made, the surface tension of each was noted, and the resulting dilutions were adjusted to pH values ranging from 4 to 9. The ionization of the depressants were noted and its relation to the pH range showing greatest efficiency was considered. The four depressants at the pH of 4 to 9 were tested against Staphylococcus aureus and Eberthella typhi so that a comparison could

be made between the effect on a Gram-positive and Gram-negative organism.

Conclusion

This study on the bactericidal and bacteriostatic action of surface tension depressants has led to the following conclusions:

1. Reduced surface tension alone does not explain the bactericidal action of a surface tension depressant possessing the latter property.

2. The bactericidal action is due to a combination of three factors or agents:

1—The surface-active material—anionic or cationic compounds.

2—The hydrogen-ion concentration of the environment—acid or alkaline.

3—The specific organisms or group of organisms—as Gram-positive or Gram-negative.

3. The bactericidal action of both the anionic compounds (Aerosol OT, Tergitol 4 and 4T) and the cationic compound (Triton K-12) is markedly influenced by the hydrogen-ion concentration. The cationic depressant, Triton K-12, exhibited its greatest efficiency in the alkaline range. The higher the pH the more efficiency did it display. The anionic depressants, Aerosol OT and Tergitol 4 and 4T, exhibited their greatest efficiency in the acid range. The lower the pH the greater bactericidal efficiency was displayed.

4. The cationic depressant, Triton K-12, generally speaking was slightly more effective against Eberthella typhi, a Gram-negative organism, as against Staphylococcus aureus, a Gram-positive organism. The anionic depressants, Aerosol OT and Tergitol 4 and 4T, were more effective against Staphylococcus aureus as compared with Eberthella typhi.

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TEST FOR HEAVY METALS IN HYPOPHOSPHOROUS ACID

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THE U. S. P. test, for heavy metals in hypophosphorous acid, is not satisfactory. The turbidity produced, by the reduction of the hydrogen sulfide in the test solution with the formation of finely divided and suspended sulfur, interferes with the turbidity reading of heavy metals. The following equation illustrates the reaction that takes place:

$$HPH_2O_2 + 2H_2S \longrightarrow PH_3 + 2H_2O + S_2$$

Heavy metals may be detected in hypophosphorous acid, in a satisfactory manner, by the following method:

Place 10 cc. of hypophosphorous acid in a small evaporating dish and add 10 cc. of hydrogen peroxide solution. Boil gently for fifteen minutes, replacing the water lost by evaporation to maintain volume. Neutralize carefully with sodium hydroxide T. S., and evaporate to dryness on a steam bath.

Dissolve 1 gm. of the crystalline residue obtained in the process described above in 50 cc. of distilled water. Carefully acidulate with diluted hydrochloric acid. Warm gently 10 cc. of this solution, contained in a test tube of about 25 cc. capacity and about 2 cm. in diameter. Add an equal volume of freshly prepared hydrogen sulfide T. S., stopper, and allow the mixture to stand at 35 degrees C. for ten minutes. At the end of this time the mixture should still possess the odor of hydrogen sulfide; if not, thoroughly saturate it with that gas and set the mixture aside again for half an hour.

The color produced, if any, is not more intense than that observed in a blank test, made in the same manner, and with the same quantities of reagents (omitting the crystalline residue to be tested), the solutions being viewed crosswise by reflected light while held against a white surface.

The test tubes in which the tests are made must be of the same diameter and must match in all respects, as closely as possible.

The hydrogen peroxide oxidizes the hypophosphorous acid to phosphoric acid and thus destroys its reducing properties. The equation for the reaction that takes place may be written as follows:

$$HPH_2O_2 + 2H_2O_2 \longrightarrow H_3PO_4 + 2H_2O$$

To prevent decomposition and volatilization when the solution is evaporated on a steam bath, the phosphoric acid is neutralized with sodium hydroxide, according to the following equation:

$$H_3PO_4 + 3NaOH \longrightarrow Na_3PO_4 + 3H_2O$$

The crystalline residue is trisodium phosphate containing the heavy metals, if any, originally present in the hypophosphorous acid. The solution is acidified with diluted hydrochloric acid to make sure that the heavy metals, if any are present, are in solution.

This test is very sensitive for all metals excepting silver. If it is suspected diluted nitric acid should be used to acidulate the solution.

American Belladonna Just as Efficient as Bulgarian in Treatment of Parkinson's Disease. In two papers presented in the *J. A. M. A. 117,* 332, 335 (1941), some very interesting results are reported on the clinical use of American Belladonna and its value in the treatment of Parkinson's disease.

Since Raeff introduced the "Bulgarian belladonna treatment" of this disease in 1926 many investigators have confirmed the efficacy of this therapy. Some workers have claimed that the roots of Bulgarian belladonna are superior to those grown elsewhere, while others have questioned this. Analyses of roots obtained from various parts of the world tend to substantiate the clinical observation that therapy is not dependent on the geographic source of the root. The alkaloidal content of the root does not differ qualitatively from region to region, although the gross appearance and total alkaloidal yield are variable.

The method of extraction of the root seeems to be of great importance. Raeff instead of employing dilute alcohol as an extractive and thereby obtaining an orthodox tincture, made a decoction of the macerated root, using white wine as a menstruum. Fabing (*Ohio State M. J. 35,* 1195 (1939)) has shown that decoctions made with 12 per cent. alcohol in one instance and white wine in the other, although giving practically identical alkaloidal yields, produced quite different pharmacologic response in animals. Apparently the method of extraction is of utmost importance in obtaining proper response to Belladonna therapy.

However, in the second paper another group of workers report their experiments and conclude that, although Belladonna is of great value in treating Parkinson's disease, its effect is due entirely to its alkaloids and little or no influence is exerted by the means of extraction employed.

WILLIAM PROCTER, JR.

By Ivor Griffith

The following is an address delivered at the exercises accompanying the unveiling of the statue of William Procter, Jr., at the American Institute of Pharmacy in Washington, D. C., May 3, 1941. Sculpted by William F. Simpson, this memorial to the "Father of American Pharmacy" is a fitting addition to the headquarters of the A. Ph. A.

ON a gloomy morning in September, 1793, the good ship "William Penn," slowly making its way through Delaware Bay and headed for Philadelphia, was stopped by a quarantine officer and the passengers were landed at Gloucester, New Jersey. This step was necessary because yellow fever was raging in Philadelphia. The travelers crossed the Delaware, skirting the center of the city, and proceeded to Germantown, thence to Morrisville, stopping on the first day of the week to attend a Friends' meeting at Fallsington. After the meeting they were invited to dine with one of the Friends. Such was the quiet hospitality of that day and age. Such too was the lavender and old lace romance of that period when one of the young men of that party, namely Isaac Procter, who had homespunned all the way from Yorkshire, England, met Rebecca Farquahar, dressed in the unpretentious but sweet habiliments of a Quaker maiden. He forthwith fell in understanding love with the young lady, and on the third day of the eleventh month, six years later, Isaac and Rebecca were at long last duly wed at the same meeting house at Fallsington.

Together they moved to Baltimore, where they resided happily and prosperously, raising a large family, the ninth and youngest child of the union being William Procter, Jr., the Junior being added to distinguish him from his Uncle William. The boy was born on the third day of the fifth month, 1817. Thus William Procter, Jr., later to become an imposing figure in American Pharmacy, was born and brought up in the city of Baltimore, where this statue which we now see was chiseled in his likeness and to his everlasting memory.

When a little over three years of age Procter lost his father, who, strangely enough, was stricken with yellow fever, the very disease which occasioned his avoidance of Philadelphia years before. Although the family had been prosperous, unexpected claims were made upon

the estate, which, although considered by the family to be unjust, were not resisted. In consequence William was deprived of the liberal education which would have befitted a mind so well calculated to receive generous instruction and which would have given additional lustre to his mature years. At an early age, therefore, he was taken from school and placed to earn a meager penny in a cooper shop, where he acquired a knowledge of tools and a dexterity in the use of them which served him many a happy turn in after life.

In 1831, at the age of 14, he entered the drug store of Henry Zollickoffer, bound by indenture as an apprentice, and was extremely happy with his work. His mother in Baltimore continued, through correspondence, to inculcate into him a spiritful and spiritual education. From one of her letters sent to him on the sixth day of the seventh month, 1831, we quote:

"Let it be thy study to endeavor to please (thy employer) not only when in the store about thy every-day business, but in everything. There are many ways of gaining the affection of those we are with by being kind and obliging to all, and if thee can lend a hand or help in any way, no matter how small the act is, never be backward, but with cheerful alacrity be always ready; this will cost thee very little, and by a kind and courteous deportment in the store and out of it thou wilt gain the love and good will of all around thee. True politeness, my son, is a lovely accomplishment, but above all, never, never equivocate to screen thyself from censure, but if thou shouldst get into any difficulty be open and candid. Let honesty and integrity be visible in all thy actions, and thus, my son, I think, thou wilt never want a friend in man, and thou wilt have a friend in thy Heavenly Father, who can, and will, if thou love Him as thou ought, do more for thee than all the world beside. Therefore, my dear boy, 'seek him now in the days of thy youth'; it is never too early to begin. There is another point on which I wish to remark—that of keeping everything thee may ever know relative to thy master's business entirely within thy own breast, sometimes by tattling or telling little matters to others it has often been a cause of a great deal of mischief and uneasiness, if not unhappiness; therefore thou wilt be guarded on this subject, never trust even thy own dear friends with anything relative to thy employer's business which thou might suppose he would not be willing for everybody to know; and always stand open to reproof, I have no doubt, if necessary, it will be administered in meekness and in love."

WILLIAM PROCTER, JR.

And what a training in human relationships is tabloided into this mother's letter to a son,—and what a challenge to the modern parent who all too often forgets that Education, really, begins at home. And it is not trite to say that the good counsels of this Christian mother were received into good ground and brought forth goodly fruit.

Procter continued to the end of his apprenticeship, manifesting much interest in the outposts of chemistry and physics and pharmacy. In March, 1837, he submitted to the Philadelphia College of Pharmacy his thesis on "Lobelia Inflata," a paper of great merit in which he demonstrated for the first time the presence of the alkaloid "Lobeline," and passed a successful examination as a candidate for the diploma of the college. He even anticipated the graduate studies of the modern curriculum by attending lectures given by Doctors Hare, Mitchell and Bache in the winter of 1840, and somewhere in his writings expressed

his amazement at the solidification of carbonic acid. Thus over a hundred years ago that commodity which now as "dry ice" functions serviceably as a refrigerant, was known and manufactured by this young worker in pharmacy. He was also greatly interested in electricity, and himself constructed an electromagnet capable of supporting several ounces.

In 1844 he opened a pharmacy, and a circular issued on opening day, bearing the date of the thirteenth day of the fifth month, carries this announcement: "In reference to that important branch of the business embracing the compounding of medicines and physicians' prescriptions, I believe that a regular education at the Philadelphia College of Pharmacy and my twelve years of experience in one of the first establishments of this city will enable me to give satisfaction." In October, 1847, he became Professor of Pharmacy at his Alma Mater, and thus initiated his active contacts with the institution and with the profession of pharmacy, contacts which he zealously and fruitfully followed to the day of his death.

For twenty-eight years Procter was associated with the AMERICAN JOURNAL OF PHARMACY as co-editor and editor, and how successfully his management was conducted is testified to by the volumes issued during that period. The original matter from his pen and his judicious selections of the foreign literature gave to the journal a value and standing among American pharmacists and made it the most complete history extant of that period of progress in pharmaceutical science in the United States. His versatility and his industry in the direction of research and in recording research are attested to by the fact that the index of the journal numbers some five hundred and fifty separate articles of his contribution, and this is exclusive of abstracts and editorials. No man of the time had such an outlook commanding the horizon of pharmaceutical literature, or whose heart was more thoroughly engaged in the work, and who was gifted with quicker perceptions or better judgment. William Procter's name will ever be associated with the progress of pharmacy in the United States, and the twenty volumes of the journal which bear his name as editor will remain an everlasting monument to his genius and zeal. He was active in so many phases of pharmaceutical practice in these fallow days that it seems impossible in the time allotted to me to cover the whole terrain of his activities.

He was one of the prime movers in the organization of the American Pharmaceutical Association. Its formative convention in the old

college building on Zane Street found William Procter, Jr., active, and indeed, from the time of the inception of this organization, he enlisted all his activity in promoting its welfare. In 1852 he was a member of its first Executive Committee, and went through several measures of service, as Corresponding Secretary, First Vice-President, and ultimately President at the session of the association which convened in Philadelphia in 1862. Yet despite all of his association work, his editorial work, caring for his business and his teaching commitments, he always found time for research. Indeed much of his work in this direction was pioneering, and had he been less backward and less modest, his reputation as a chemical researcher might have transcended his magistry in pharmacy. He was recognized in the contemporary literature of the continent as one of the outstanding American pharmaceutical chemists, and his contributions were in the diversified fields of plant, and animal, and metallic chemistry. In evidence of this widespread scope of his work, a brief list of his papers is herewith printed:

In 1838, a paper "Demonstrating the existence of amygdalin in several species of the genera *Prunus* and *Amygdalus.*"

In 1839, "Observations on dextrin and diastase," and "On *Lobelia cardinalis,*" showing the presence in that plant of an alkaloid different in some respects from the alkaloid found in *Lobelia inflata.*

In 1840, a paper "On the power of saccharine substances in protecting from decomposition solution of protiodide of iron."

In 1841, an essay "Supplementing his thesis on *Lobelia inflata,* and showing that the alkaloid therein described, represents the plant in medicinal qualities."

In 1842, "Observations on the volatile oil of *Gaultheria procumbena,* proving it to be a hydracid analogous to salicylous acid."

A year later, M. August Cahours took up the same subject, and arrived at the same results by a proximate analysis of the oil, but in his paper, published in the *Journal de Pharmacie et de Chimie,* March, 1843, he makes no allusion to Mr. Procter's previous publication, leaving us uncertain whether he had seen Mr. Procter's paper, or whether the investigation made by him was coincident with that of Mr. Procter.

In 1843, "On the volatile oil of *Betula lenta* (sweet birch) and on gaultherin"—a substance playing a part similar to amygdalin—and which, by its decomposition, yields an oil identical with oil of gaultheria.

In 1847, "On the reduction of oxide of iron by hydrogen."

In 1849, "Remarks on the oleo-resinous ethereal extracts, their preparation, and the advantages they offer to the medical practitioner."

In 1851, among numerous contributions, we have an essay "On the botanical and chemical character of sassy bark (the doom plant) of Western Africa."

In 1852, a continuation of the essay on sassy bark, and "Observations on the volatility and solubility of cantharidin, in view of an eligible pharmaceutical treatment of Spanish flies."

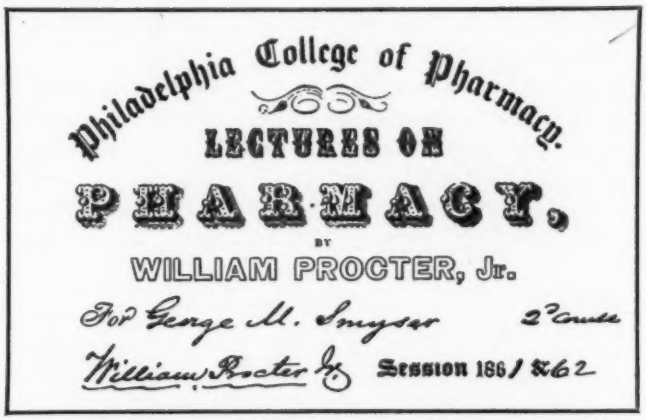
In 1853, fluid extracts began to attract attention, and in this and the succeeding year he contributed several papers on that subject; also, one "On the pharmacy of the phosphates."

In 1858, "An essay on the hypophosphites."

In 1859, "On polygalic acid," and "On the existence of nicotine in green tobacco." In the same year, he read before the American Pharmaceutical Association, in Boston, an elaborate essay on fluid extracts, suggesting formulas for their preparation, and presented specimens of over thirty fluid extracts prepared according to his suggested formula.

Indeed in the entire field of American Pharmacy, throughout the decades of its existence, no one has presented the many-faceted talents that were present in this one man, and it is scarcely strange that because of his unceasing industry and constant mental exercise, his rather frail physical vessel did not long endure. He died at the early age of fifty-six, mourned by all who knew him. On a Tuesday afternoon in February, 1874, with the wild winds of winter hurling snow against the window panes on the second floor of the small new school on Tenth Street, Dillwyn Parrish, in somber Quaker garb, addressed the College membership. Said he: "On Tuesday morning, the 10th inst., the intelligence was spread among us that Professor Procter had died during the night. So overwhelming was the sense of the loss we had sustained, that our hearts were mute with grief.

"Slowly, but not with less impressiveness, comes to us the realization that the voice, so lately heard in instruction and in counsel within these walls, is now sealed in death. While mourning a loss which seems to us almost irreparable, it is fitting that we should call to remembrance the many benefits which the life of our brother has bestowed upon us. For a quarter of a century his name has been inscribed on our banner, and we have found it a talisman of strength.



CARD OF ADMISSION TO PROCTER'S COURSE IN PHARMACY 1861-62

"His life was characterized by earnestness of purpose, single-minded in pursuit of science, sincere, in all his relations in life, loving Truth for Truth's sake; his enemies are unknown, but friendship is claimed wherever his name is spoken.

"The record of his life is engraved on the character of this institution, whose journal is an enduring monument of the activity and ability of his genius. His name comes back to us from beyond the Atlantic in pharmaceutical literature with acknowledged authority. Well may the drapery of mourning be hung upon these walls, and our eyes turn in depressing sadness to the vacant chair."

William Procter, Jr., had lived in those staid and steady Philadelphia days when, in between the cobble stones, the grass grew green on High Street—and the wood thrush still maintained his nest—and sent his merry song winging through the blue above the crystal Schuylkill creek.

It was the golden, quiet Quaker age of Philadelphia town—when even progress moved on silent wheels and the gentle hand of peace was on the land and people.

They were the days, before the whirlwind—those mellow, fallow days when art was strangely short and time not half so fleeting.

Such were the days—and there the place, where William Procter worked, in serious Quaker company—with diligent and forward-looking minds—not merely marking time of day and strengthening their present, but striving, earning rich tomorrows for us, their children yet unborn.

How unlike now, when government by man promptly views bad debts—instead of better deeds—to pile against posterity.

The Quaker way was a different way, and Procter was a Quaker.

Here in Washington, this day, while the dust of Procter rests in a quiet New Jersey green acre of God, we meet to make solid his memory, and it is meet and right to erect statues to our honored dead, lest we forget, yet Procter's greatest monument must ever be his great and various services to Pharmacy, and to the other sciences serving Public Health.

And may I conclude this note of a great man's life and his entitlement to a long remembering with this inspiring, inspired challenge from the pen of the great Carlyle:

> "Could each here vow to do his little task as the one whom we now honor did his great one—in the manner of a true man—not for a day, but for the ages; to live as he counseled, not commodiously in the Reputable, the Plausible, the Half; but resolutely in the Whole, the Good, and the True."

Safeguards Needed in Treatment of Gonorrhea With Sulfonamides. C. A. W. Uhle, L. W. Latowsky and F. Knight, in the *J. A. M. A. 117,* 247 (1941), discuss the present treatment of gonorrhea with the sulfonamides as to certain new dangers introduced. When first inaugurated this treatment seemed to promise Utopia to the physician and patient, but sufficient evidence has now been accumulated to point out the fallacy of such first impressions. If gonorrhea is to be kept from becoming an even greater menace certain facts must be appreciated.

The authors have studied the effectiveness of chemotherapy in two parallel groups of cases. All were ambulatory and in one group sulfapyridine was employed, whereas in the second sulfathiazole was used. Sulfapyridine effected cures in 92 per cent. of the cases and required from 14 to 162 days for complete cures to be accomplished. Sulfathiazole gave cures in 96 per cent. of the cases and from 7 to 28 days were required. Thus cure is not immediate or instantaneous as might be supposed and this is particularly hazardous since the disappearance of symptoms within a few days of treatment may give rise to a real public health problem in the form of the asymptomatic carrier. The tendency of ignorant or indifferent patients to default and not continue treatment due to the disappearance of all discharge must be recognized and prevented if possible by the personal efforts of the physician. The authors point out the unreliability of smear examination as an absolute indication of cure and recommend proper culturing technic as the only basis upon which positive pronouncement of cure can be made. A combination of sulfonamide by mouth and local treatment is considered to be the best form of management.

PHARMACOPŒIAL DELETIONS

Articles official in the U. S. P. XI, but not to be admitted to the U. S. P. XII

Acetyltannic Acid and Albumin Tannate—Have not proved efficient as intestinal astringents. There is evidence that high up in the small intestines the tannic acid is changed to sodium gallate, which is not astringent. Neither tannic acid nor gallic acid appears in the feces. Any astringent action is likely to be exerted in the stomach or duodenum rather than in the intestines lower down.

Aconite, Tincture of Aconite—In fever it has been supplanted by strikingly better remedies. As a vagus stimulant it is not employed, probably because of its lack of certainty, or its lack of safety in the necessary doses.

Acriflavine and Acriflavine Hydrochloride—It was employed extensively in World War I, but since that time its use has steadily declined. It is bacteriostatic rather than bactericidal. Recommended to replace iodine as an application to the skin in preparation for operation, it has been refused acceptance by many surgeons. Similarly in infectious and ulcerative conditions of mouth, bladder, vagina and rectum, its use has steadily declined. The Sub-Committee on Surgical Infections of the National Research Council has repudiated it on the ground that it is ineffective in the treatment of wounds.

Ammonium Benzoate, Bromide and Salicylate have been used in the fallacious belief that the ammonium radicle is in some way protective to the heart. Ammonium salts are less stable and unnecessary duplicates of the corresponding salts of potassium and sodium.

Many criticisms have arisen with regard to the proposed deletion of certain U. S. P. XI drugs from the coming edition of the Pharmacopœia. The Revision Committee has released the accompanying information, summarizing the basis of such decision by the subcommittee on scope, and it is printed here because of the interest it holds for every pharmacist.—Ed.

Aromatic Sulfuric Acid—Formerly used extensively as a solvent for quinine sulfate, and now obsolete.

Arsenic Triiodide—Undesirable to administer both arsenic and iodine in a fixed salt of this type.

Asafetida, Emulsion of Asafetida—Its value in hysterical conditions is questionable. Its use by mouth for flatulency is not justified by results. Its use by rectum in tympanites can be duplicated by pleasanter smelling and more effective agents.

Bismuth Subgallate—It has no advantages over the subcarbonate. Because of the presence of gallic acid, it has produced the erroneous idea that it is astringent.

Calcium Bromide—An unnecessary duplicate with no therapeutic advantages over other bromides.

Calcium creosotate, creosote, creosote carbonate, guaiacol and other creosote relatives are neither antiseptic in the respiratory tract nor expectorant. The local antiseptic value of creosote in a tooth cavity and its deodorizing value in pulmonary tuberculosis were not considered justification for its continuation in the Pharmacopœia.

Cannabis, Fluidextract of Cannabis, Extract of Cannabis—A little used drug, very variable, and with the easily produced undesirable effects characteristic of marijuana indulgence.

Cantharides, Cantharides Plaster, Tincture of Cantharides—Employed essentially as a local irritant and blistering agent. Blisters have fallen into disuse. As an irritant in scalp lotions and otherwise, the remedy is superfluous.

Capsicum, Tincture of Capsicum—A local irritant with extensive use, but not considered important enough for the Pharmacopœia.

Carbromal—A mild sedative, closely related to and differing little from the extensively used and better known barbiturates. The amount of bromine in a dose is altogether too small to give a bromide action.

Cinchona, Compound Tincture of Cinchona—As antimalarial no longer employed. For the purposes of a bitter, remedies just as effective but simpler are available.

Compound Mixture of Opium and Glycyrrhiza—Brown Mixture represents what now is looked upon as an almost extinct type of galenical. In teaspoonful doses, its antimony and opium are too little to be therapeutically effective.

Compound Powder of Senna (Compound Licorice Powder)—As a senna preparation it is complicated by the presence of sulfur, which gives an unduly soft consistency to the stools, and often a very offensive odor.

Copaiba—An old time urinary antiseptic, bad tasting and irritating to the stomach and kidneys. It is not a very effective antiseptic in the urinary tract, and simpler and better drugs for the purpose are available.

Dichloramine-T and Dakin's Solution—Dichloramine-T, the oil-soluble chlorine furnisher, and Dakin's solution (diluted solution of Sodium Hypochlorite) were deleted on the ground of their proven inefficiency. The water-soluble Chloramine-T was retained. For the slow and steady elimination of chlorine, Azochloramid in triacetin solution was considered superior and was admitted. The latter is now being extensively employed in Britain in preference to other chlorine antiseptics.

Diluted Acetic Acid was a "pharmaceutic necessity" in the manufacture of Solution of Ammonium Acetate and Vinegar of Squill, both of which have been deleted.

Elixir of Glycyrrhiza—The Syrup of Glycyrrhiza was substituted for the elixir on the basis of its more extensive employment and its freedom from alcohol.

Ethylhydrocupreine Hydrochloride—Introduced for the treatment of pneumonia, it has proved too toxic for oral or parenteral use, and ineffective. It is still employed as a local application in pneumococcal infections of the eye but for this use it is rapidly being supplanted.

Extract of Nux Vomica—Of no use as a bitter, and for a strychnine effect it is more rational to employ strychnine salts.

Fluidextract of Belladona Root—The exclusion of this follows the general principle that, where the dose is very small, such concentrated liquid preparations as fluidextracts are undesirable. It was formerly retained for the preparation of Belladonna Liniment, but this is no longer a Pharmacopœial preparation.

Iodoform—Vile-smelling and of low rating as an antiseptic. It is rapidly being replaced by more effective agents which lack the disagreeable odor.

Iron—This was elementary iron, in the form of fine bright wire, filings or powder. It was used in the preparation of Syrup of Ferrous Iodide which has been deleted.

Kino, Tincture of Kino—A tannic acid remedy, which does not reach the lower intestines as such.

Magma of Ferric Hydroxide—It was introduced as an arsenic antidote. At best it is not very efficient, and there are conflicting reports as to any efficiency at all.

Mass of Mercury (Blue Mass)—Now considered an obsolete mercury galenical preparation.

Merbaphen—Its use has been largely abandoned in favor of the less toxic and more effective Salyrgan, which is now admitted to the Pharmacopœia.

Nutgall, Nutgall Ointment—This is employed for its tannic acid, and preparations of the latter are to be preferred.

Oil of Santal—Irritating to the stomach and kidneys, and not a powerful antiseptic in the urinary tract. Much more effective chemical remedies are now available.

Pepsin—A powerful enzyme that is superfluous in therapeutics. For the digestion of protein it acts best in an acid medium of pH 1.5 to pH 2.5, and does not act at all in a medium above pH 4.0 to 4.5. In gastric achylia the needed acidity cannot be obtained in the stomach by any doses of acid that it is possible for a patient to swallow.

Pills of Aloe—Drastic cathartics no longer have Pharmacopœial approval. However, Aloe itself as been retained, and also Aloin, which is not drastic.

Podophyllum, Resin of Podophyllum—Also a drastic cathartic. Drastics are irritant to the whole alimentary tract, from the stomach down. If catharsis fails to take place, they are capable of producing inflammation of the intestines, and, after absorption, of the kidneys.

Potassium Chlorate—An antiquated mouth astringent. Any internal use for it is not justified.

Powder of Ipecac and Opium—Its main use is to produce sweating and sleep. Its ability to induce copious sweating depends mainly upon the hot drinks with which it is administered and the heavy covering of bed-clothes. The ipecac is nauseating, and in this powder can scarcely be said to be used for its expectorant value. The opium is simply "dope," to be better prescribed by itself if it is desired.

Pyrogallol—Not now much used as an antiseptic in therapeutics.

Quinine—This is the pure alkaloid, as distinguished from its salts. It is not used in therapeutics, and is not required as a "pharmaceutic necessity."

Santonin—As an anthelmintic it has given place to newer remedies.

Serpentaria—This was a "pharmaceutic necessity" in the preparation of Compound Tincture of Cinchona, which has been deleted.

Sodium Acetate—The potassium salt is preferred and much more in use.

Solution of Ammonium Acetate—Believed to be of no therapeutic value.

Solution of Ferric Chloride, Tincture of Ferric Chloride—The solution was required for the preparation of the Tincture. As an anti-anemia remedy the tincture has been largely supplanted by iron preparations that do not injure the teeth and are less astringent.

Solution of Iron Tersulfate—Formerly used as a hemostatic, this makes a nasty mess when mixed with blood, and is locally irritating and even corrosive.

Spirit of Chloroform—Not desirable as a sedative and not needed as a carminative.

Spirit of Ethyl Nitrite—Not effective as a nitrite, and has no distinctive therapeutic properties.

Squill, Syrup of Squill, Tincture of Squill, Vinegar of Squill—Squill lacks the highest approval as a cardiac drug. Its use as an expectorant is based on erroneous observations.

Strychnine Nitrate—On account of the efflorescence of the sulfate, the nitrate was admitted to the last revision as a stable salt. However, it has not come into favor, and it was considered unnecessary to admit two strychnine salts.

Sulfonethylmethane—The limitations and disadvantages of "Trional" as a hypnotic have greatly lessened its use.

Syrup of Ferrous Iodide—Unsatisfactory as a means of administering either iron or iodine. The dose of each should be separately considered.

Terebene—Neither antiseptic in the respiratory tract, nor valuable as an expectorant.

Theobromine with Sodium Salicylate—Theobromine with Sodium Acetate is considered better, and it eliminates the chance of harm to diseased kidneys from the salicylic radicle.

Valerian, Tincture of Valerian—Believed to be an overrated drug in hysteria, and too malodorous as a carminative.

Veratrum Viride, Tincture of Veratrum Viride—A dangerously toxic drug, highly variable, and very little used. Its chief employment is in eclampsia, in which extremely large (and dangerous) doses are recommended by its advocates. Reports from many noted obstetricians are not favorable to its use in eclampsia.

Washed Sulfur—Three forms of sulfur were deemed unnecessary for the Pharmacopœia. Precipitated Sulfur and Sublimated Sulfur are retained.

Yellow Mercurous Iodide—Formerly extensively administered as an oral antisyphilitic, this remedy has been supplanted by more desirable remedies.

OUR CONTRIBUTORS THIS MONTH

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SELECTED ABSTRACTS

From Current Literature

Cadmium Metal Poisoning. J. T. Cangelosi. *U. S. Naval Med. Bull. 39,* 408 (1941). The use of cadmium plated food utensils in the Fleet Marine Force has resulted in 208 cases of acute poisoning. In each case the symptoms were of brief duration and recovery was rapid. In each instance the food causing illness had been in contact with the utensil for a considerable time (1½-14 hours). In one lot of food, namely lemonade, the cadmium content was found to be 100 p. p. m. Fifteen parts per million have been found to produce mild toxic symptoms.

Sodium Carbonate in the Treatment of Vincent's Infection. S. L. Rosenthal. *J. A. D. A. 28,* 972 (1941). Recent experiments have shown that it is the presence of sodium carbonate in the saliva of animals which contributes to their immunity to Vincent's infection. Man lacks this constituent, since the carbonate in his saliva occurs as bicarbonate. The topical application of sodium carbonate has been shown effective in Vincent's infection. The present author reports the results of *in vitro* experiments, those results obtained with animals, and clinical results.

Since the phenol coefficient test is not applicable for testing oral antiseptics, an *in vitro* test based on loss of motility was devised. It has been shown, for example, that loss of motility with other species results in loss in pathogenicity and an analogous condition was considered in the case of these organisms. A 10 per cent. solution of sodium carbonate penetrated debris rapidly and stopped motility instantly. Weak solutions were equally efficient against exposed organisms but they failed to penetrate the debris and therefore bacteria protected by such material are not subjected to the action of the solution. Ten per cent. solutions also inhibited the growth of the non-motile organisms.

Clinical treatment involved the local application of a 10 per cent. solution making sure that the solution reached the bottom of all pockets and that the entire gingivæ were moistened. The tissues were thus kept moist ten minutes, the patient dismissed and instructed to use a 1 per cent. solution as a mouth wash. Twelve dentists employed this technic in 145 cases with successful results in each case. Ten

instances of sore tongue and gums were observed. In some of these the use of the deka-hydrated salt $Na_2CO_3.10H_2O$, which due to impurities is objectionable, was considered a factor. The monohydrated (U. S. P.) should be the salt employed.

Local Applications of Sulfanilamide. *Pharm. J. 92,* 257 (1941). Goodwin and Findlay of the Wellcome Bureau of Scientific Research have reported in *Lancet,* 1941, i, 691, their results in applying three representative sulfonamides to uninfected wounds in rabbits. They found that sulfanilamide was absorbed and excreted more rapidly than either sulfapyridine or sulfathiazole. There has been an increased interest in the use of sulfanilamide locally. Originally it was simply dusted on the wound or the cavity plugged with gauze on which the dry drug had been liberally sprinkled.

More recently the incorporation of sulfanilamide into various bases has been practiced and in this connection the results of Locatelli and Bowden are of considerable interest. They have shown that the nature of the base employed will alter the degree of action on bacteria. Apparently there is little to choose between the relative value of the powder and its dispersion in olive oil, liquid petrolatum and glycerin, although a 30 per cent. mixture with glycerin produced a slightly larger area of bacterial stasis than any of the other forms. A mixture of the sulfanilamide in simple ointment resulted in an inactive combination according to the test employed. This observation is of interest to those in the United States who commonly use simple ointment (wool fat, white wax and white petrolatum) as a base. The decided inhibitory action of this base should lead to the choice of one which would prove more suitable.

The Stability of Morphine Solutions. *Pharm. J. 92,* 231 (1941). In England one often hears the comment that the most important component of a first aid kit during rescue operations is a solution of morphine.

In many instances the infrequent use of the solution requires its preservation to prevent inactivation. H. Berry (*The Public Pharm. 2,* (1941) has recommended the use of potassium metabisulfite to prevent oxidation. Discoloration develops more readily in alkaline solution and is retarded by acid, but if the pH is less than 3.0 some

discomfort is experienced by the patient on injection. Morphine solutions of about pH 2.7 are stable on heating and over long periods of storage if the development of color is regarded as the criterion of stability. If autoclaving cannot be carried out it is advisable to add 0.2 per cent. *p* chlor-*m*-cresol and to steam thirty minutes.

As solutions of metabisulfite become acid on heating, it is advisable to use the minimum of heat during sterilization. The following formula is recommended:

Morphine salt	2.5 %
Potassium Metabisulfite	0.05%
P-chlor-*m*-cresol	0.20%
Water to make	100

The solution, which has a pH of about 4.0, is sterilized by steaming for thirty minutes in sealed ampuls or in a sealed vaccine bottle.

Luminescent Materials and Their Wartime Uses. *Chem. & Ind. 60,* 551 (1941). During the early stages of the war in England considerable disappointment resulted due to the inefficient operation of many types of appliances and apparatus utilizing the principle of luminescence. This paper is based on Bulletin C-17, dealing with luminescent materials and their wartime uses, issued by the Ministry of Home Security, Research and Experiments Department. It is the object of this bulletin to present a reliable appraisal of this field and its possible applications. Two types of luminescent materials are recognized: Type "A" materials, which have a high brightness during and for a short time after irradiation, and Type "B", which have a lower brightness during and after irradiation than Type "A", but which have a longer afterglow.

A number of fluorescent and phosphorescent materials are discussed from the standpoints of effectiveness, proper method of application, etc. The means of excitation are described, including daylight, black-bulb mercury vapor lamps, argon glow lamps and tungsten lamps with black glass filters.

A list of applications of this principle are described such as A. R. P. signs, instrument boards, shelter entrances, signs and obstruction markings, articles of wear to prevent pedestrian collisions and various emergency signs. The valuable experience gained in this important field of civilian protection should be of interest to many workers both in defense planning as well as commercial fields.

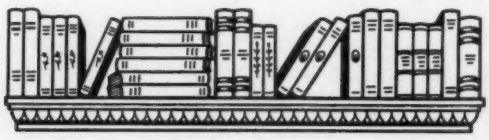
BOOK REVIEW

A New Volume Is Brought to Your Attention

The American Illustrated Medical Dictionary. A complete dictionary of the terms used in medicine, surgery, dentistry, pharmacy, chemistry, etc., with pronunciation, derivation and definition. By W. A. Newman Dorland, A. M., M. D., F. A. C. S., with the collaboration of E. C. L. Miller, M. D. 19th Edition, 1647 pages, 914 illustrations. W. B. Saunders Co., Philadelphia and London, 1941. Price: Plain, $7.00; thumb-indexed, $7.50.

To those interested in any phase of medical science, Dorland's Medical Dictionary is almost an institution. With a background of four decades, this latest edition maintains the same high quality of lexicography for which this work is noted.

During the three years since the advent of the eighteenth edition, considerable progress has been made in chemotherapy, endocrinology, vitamin therapy, psychiatry and other fields of medicine. In keeping with these advances, some 2000 new words have been added to this present volume.

Although broad in its scope and coverage, the book is of convenient size for desk use, enabling one to make quick and ready reference. The student and practitioner of medicine, dentistry and pharmacy will find this an almost necessary addition to his library.

L. F. T.